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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,288	02/19/2002	Shiao-Wen Tsai	BHT-3111-234	1092

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DOUGHERTY & TROXELL  
SUITE 1404  
5205 LEESBURG PIKE  
FALLS CHURCH, VA 22041

EXAMINER
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MOHAMED, ABDEL A

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/076,288	TSAI ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Abdel A. Mohamed	1653	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 December 2004.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 25-47 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25-47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### **ACKNOWLEDFMENT OF AMENDMENT, REMARKS, STATUS OF THE APPLICATION AND CLAIMS**

1. The amendment and remarks filed 12/1/04 are acknowledged, entered and considered. In view of Applicant's request the substitute specification has been entered, claims 1-24 has been canceled and claims 25-47 have been added. Claims 25-47 are now pending in the application. The objection to the specification, claims and abstract, and the rejections under 35 U.S.C. 112, second paragraph and 102(b) are withdrawn in view of Applicant's submission of substitute specification, amendment, remarks, cancellation of claims filed 12/1/04. However, the rejection under 35 U.S.C. 103(a) over the prior art of record is maintained.

### **ARGUMENTS ARE NOT PERSUASIVE**

#### **CLAIMS REJECTION-35 U.S.C. § 103(a)**

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Newly submitted claims 25-47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Silver et al (U.S. Patent No. 4,970,298) taken with Feijen (U.S. Patent No. 5,041,292) and Silver et al (U.S. Patent No. 4,703,108).

Applicant's arguments filed 12/1/04 have been fully considered but they are not persuasive. It is noted that Applicant has canceled claims 1-24 and instead presented claims 25-47. Applicant's arguments that the primary reference of Silver et al '298 patent discloses a method for the preparation a collagen-based sponge, in which the disclosed method is conducted in water without any organic solvent. Accordingly, a cross-linked cluster matrix could not be subjected to further cross-linking reaction and the prepared matrix is not homogeneous. In the examples set forth in '298 patent, no organic solvent is included in the preparation of the collagen-based sponge, and the '298 patent is directed toward the concept of producing a sponge-matrix, in contrast to Applicant's method which produces a bio-compatible matrix in various shapes as desired is unpersuasive.

Contrary to Applicant's arguments, the primary reference of Silver et al '298 patent discloses a method for the producing cross-linked protein-polysaccharide bio-composite comprising a collagen-based solution or an insoluble collagen dispersed and swollen in suitable liquid media (e.g., dilute hydrochloric acid, dilute acetic acid or the like) at a pH between 3.0 and 5.0 and is subjected to a temperature of between 0<sup>0</sup> C to -100<sup>0</sup> C to thereby solidify the collagen-based material. The solidified collagen-based material is subjected to a vacuum of less than about 50 millitor at a temperature of from about 22<sup>0</sup> C to -100<sup>0</sup> C to form a collagen based sponge or the collagen-based dispersion is dried into sheet form at temperatures of from 4<sup>0</sup> C to 40<sup>0</sup> C for a period of time of from 2 to 48 hours. The collagen-based sponge or sheet is contacted with cross-linking agent of a carbodiimide which include 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, wherein the collagen-based sponge or sheet is immersed in a carbodiimide solution at a concentration of from about 0.1 to 10% (W/V) and maintained at a temperature of from about 2<sup>0</sup> C to 40<sup>0</sup> C and at a pH of between 2 to 11 for a period of time of from about 2 to 96 hours to form the collagen-based matrix. The carrier compound (intermediate) polysaccharide such as hyaluronic acid are incorporated during the initial processing steps in forming the collagen-based sponge or sheet, or after cross-linking of the intermediate collagen-based matrix or after mixing with collagen during dispersion, prior the cross-linking steps (See e.g., cols.4-6, Examples 4, 8 and 11) as directed to claims 25-28, 30-32, 34-36 and 40-44. On col. 7, lines 1-4, the '298 patent states that a film 0.5 to 1.5 mm in thickness is applied to the matrix layer and is allowed to cure at a room temperature for at least 2 hours using a vacuum of 14

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in of Hg, which overlaps with the claimed matrix thickness of 50  $\mu$ m-1mm thickness of claim 14. Further, as to the limitation using organic solvents such as ethanol of claims 38, 45 and 46, the '298 patent discloses using organic solvent such as ethanol in the process of producing a collagen-based matrix. Also, on Example 1, the reference discloses the use of acetic acid and NaCl in the process of preparing soluble and insoluble collagens, and as such meet the limitations of claims 28 and 33. Thus, the primary reference of '298 patent clearly teaches a method of producing a bio-compatible matrix in a desired shape which is a collagen-based sponge or sheet.

With regard to Applicant's allegation that it is basic principle of patent law that is improper to arbitrarily pick and choose prior art patents and combined selected portions of the selected patents on the basis of Applicant's disclosure to create a hypothetical combination which allegedly renders a claim obvious, unless there is some direction in the selected prior art patent to combine the selected teachings in a manner to negate the patentability of the claimed subject matter and cites *In re Rothermal and Waddell*, 125 USPQ 328 (CCPA 1960) is unpersuasive. Contrary to Applicant's allegation, the primary reference of Silver et al '298 patent differs from claims 25-47 in not teaching the weight ratio of polysaccharide and protein which is in the range of 20/80 to 80/20 and use of a buffer solution of phosphate and NaCl having a concentration of 0.15-4M. However, the secondary reference of Feijen et al discloses a biodegradable hydrogel matrix comprising a protein, a polysaccharide such as chondroitin sulfate and a cross-linking agent, wherein the cross-linking agent is a carbodiimide, preferably a water-soluble carbodiimide N-(3-dimethylaminopropyl)-N-ethylcarboimide (EDC). The cross-

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linking agent is added to an aqueous solution of the polysaccharide and protein, at an acidic pH. The cross-linking agent providing network linkages there between, wherein the weight ratio of polysaccharide to protein in the matrix is in the range 10:90 to 90:10 which overlaps with the claimed ranges of 20/80 to 80/20 (See e.g., cols. 2-4, Example 1, claims 1, 6 and 12) as directed to claims 25, 26, 40 and 41. Further, the secondary reference of Silver et al '108 patent discloses the formation of a sponge or a sheet of collagen-based matrix incorporating polysaccharide such as hyaluronate, wherein the soluble collagen is dissolved in a suitable solvent, such as dilute HCL acid, dilute acetic acid or the like (See e.g., cols. 3-4) as directed to claim 28. On Example 19, the reference teaches the use of buffer solution having a concentration of 0.182M phosphate and 0.154M NaCl, which overlaps with the buffer salt concentration of 0.154M of claim 47.

Further, Applicant concludes by arguing that it is believed to be well established that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. Contrary to Applicant's arguments, the combined teachings of the prior art clearly teaches a method for producing biodegradable collagen-based matrix in desired shape of sponge or sheet form, wherein polysaccharide such as hyaluronic acid and collagen are added to a dilute HCl solution of pH 3. The solution is poured into a vacuum flask and de-aerated (degassed) at a vacuum, and then cross-linked with carbodiimide and allowed to air dry or freeze dry for a period of time under suitable conditions to form the collagen-based matrix. Therefore,

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in view of the above, the combined teachings of the prior art makes *prima facie* obvious the claimed invention's method for the producing cross-linked polysaccharide-protein bio-composites such as cross-linked hyaluronic acid-collagen biocomposites, particularly, to homogenous solution that is formed by various concentrations of hyaluronic acid-protein, and can be processed to different types of the bio-composites as claimed in claims 25-47.

Thus, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the combined teachings of the prior art method would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Best*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

### **NEW GROUND OF OBJECTION TO THE SPECIFICATION AND REJECTION TO THE CLAIMS**

3. The followings are new grounds of objection and rejection necessitated by Applicant's amendments:

#### **NEW MATTER OBJECTION TO THE SPECIFICATION**



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4. The extensive amendment to the specification filed 12/1/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the extensive amendments on pages 1-6 and 9-24, the addition of new matter on pages 3, 11 and 12 by broadening the scope of the invention, change of the language and rearrangement of the specification by deletion and insertion. For example, there is no support in the originally filed disclosure for **"for preventing tissue from sticking after surgery"** as disclosed on page 3, line 17; no support as originally filed for **"non-toxic, and impalpable"** as recited on page 11, last paragraph, line 8; no support as originally filed for **"a pH of from 4 to 4.5 at a temperature of from 20 to 45°C for a period of 1 to 6 hours, preferably 2 to 4 hours"** as disclosed on page 12, step (d), lines 3-5; and there is no support as originally filed for **"and a mixture thereof"** as recited on page 12, last line.

#### CLAIMS REJECTION-35 U.S.C. 112, <sup>2nd</sup> PARAGRAPH

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 27-29, 41 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is indefinite and confusing in the recitation "wherein the protein in the step (b)" because there is no protein solution recited in step (b) of claim 25.

Amendment of claim to 27 to recite "wherein the protein solution in the step (a)" is suggested.

Claims 27-29, 41 and 47 are indefinite in the recitation "a mixture thereof" because it is unclear as to the amounts of the components in the mixtures, which components, and what are the mixtures? Appropriate clarification is required.

**ACTION IS FINAL, NECESSITATED BY AMENDMENT**

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

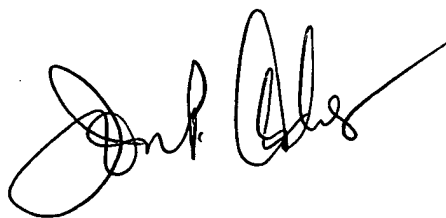
### CONCLUSION AND FUTURE CORRESPONDANCE

7. No claim is allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272 0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



**JON WEBER**  
**SUPERVISORY PATENT EXAMINER**

 Mohamed/AAM  
February 14, 2005